PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PA111-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2005/000693	International filing date *(day/month/year)* 25 January 2005 (25.01.2005)	Priority date *(day/month/year)* 29 January 2004 (29.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant QIAGEN GMBH		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 03 October 2006 (03.10.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt11@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference PA111-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000693	25.01.2005	29.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/10

Applicant
QIAGEN GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I **Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-22	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-22	NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims		NO

2. Citations and explanations:

1 Subject matter of the application

The present application claims a chromatographic separation process for fractionating nucleic acid mixtures. Plasmid DNA in particular can be separated off from other nucleic acids such as RNA by means of this process, by applying the mixture to an anion-exchange matrix and subsequently eluting it with different salt concentrations.

2. Documents

This opinion makes reference to the following documents (D) cited in the International Search Report; the same numbering will be used throughout the procedure:

D1: WO 01 38516 A (STADLER JOACHIM; Q ONE BIOTECH LTD (GB); AMERSHAM PHARM BIOTECH AB) 31 May 2001 (2001-05-31)

D2: US-A-5 990 301 (COLPAN METIN ET AL) 23 November 1999 (1999-11-23)

D3: WO 96 21177 A (QIAGEN GMBH; COLPAN METIN (DE); MORITZ PETER (DE); SCHORR JOACHIM) 10 August 1995 (1995-08-10)

D4: US-A-5 057 426 (HENCO KARSTEN ET AL) 15 October 1991 (1991-10-15)

D5: FERREIRA G N M ET AL: 'Downstream processing of plasmid DNA for gene therapy and DNA vaccine applications' TRENDS IN BIOTECHNOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 18, no. 9, 1 September 2000 (2000-09-01), pages 380-388, XP004214265 ISSN: 0167-7799

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D6: PRAZERES D M F ET AL: 'Large-scale production of pharmaceutical-grade plasmid DNA for gene therapy: problems and bottlenecks' TRENDS IN BIOTECHNOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 17, no. 4, April 1999 (1999-04), pages 169-174, XP004162836 ISSN: 0167-7799

D7: STADLER JOACHIM ET AL: 'Plasmid DNA purification.' THE JOURNAL OF GENE MEDICINE. ENGLAND FEB 2004, vol. 6 suppl. 1, February 2004 (2004-02), pages S54-S66, XP002272777 ISSN: 1099-498X

3. Inventive step (PCT Article 33(3))

The subject matter of claims 1-22 does not involve an inventive step within the meaning of PCT Article 33(3) for the following reasons:

3.1 Document D1 likewise describes a process for purifying plasmid DNA by means of anion-exchange (AIEX) chromatography. This process comprises the following process steps:

Adsorption:
The adsorption of the mixture to be separated on the AIEX material is effected under pH conditions which lead to a negative charge on the nucleic acid material (recommended value about 5.1). The conductivity of the buffer/medium should be set to an appropriately high value in order to aid later desorption and to increase the selectivity between RNA and plasmid. However, the conductivity should be below the maximum conductivity at which the plasmid DNA is still bound to the AIEX material (page 8, lines 14-33).

Desorption:
The desorption of the bound material can be effected by increasing the buffer conductivity, the pH or by a combination of both steps. An increase in the conductivity is achieved by rising salt concentrations in the elution buffer (page 10, lines 21-30). Alkali metal halides (LiCl or NaCl) are mentioned as suitable salts.

When these steps are followed, the following elution pattern can, according to D1, be achieved:

a) the major part of the RNA in the initial eluate or in the washing fraction (if carried out)
b) small proportion of RNA in the initial part of the conductivity gradient
c) elution of the plasmid as a defined peak in the further course of the conductivity gradient.

Furthermore, it has to be noted that neither RNAses nor alcohol/solvent-containing buffers are used in the process according to D1 (see experimental part of D1).

The process described in D1 is therefore equivalent to the method described in claim 1 of the present application. An inventive step for the choice of the specific parameters which are defined in the claim cannot be established at the present point in time. Consequently, the method of claim 1 is not inventive within the meaning of PCT Article 33(3).

3.2 Dependent claims 2-16 and 17-22 do not contain any additional features which require an inventive step. Rather, they relate to adaptations of the parameters used which do not demand any inventive activity from a person skilled in the art.

3.3 Claim 16 relates to a specific functional group of the AIEX material. However, precisely this group has already been described in D2 and D3 (likewise by the applicant). Both documents indicate that this column material is particularly well-suited to the separation of DNA and RNA (e.g. D2: column 4, lines 60/61). No inventive step can therefore be acknowledged in the use of this material, either.

3.4 Furthermore, it has to be pointed out that, according to claim 1, buffers having a particular ionic strength of monovalent **and/or** divalent salts can be used for elution of the

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

nucleic acids. However, since the conductivity of the buffer has considerable differences depending on whether both salts are used in the indicated concentration or only one of the two is used, there are justified doubts as to whether the technical effect claimed can be achieved in **both** cases.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

4. PCT Article 5/6

4.1 Claim 1 relates to the use of any chromatographic carrier material. However, it is obvious to a person skilled in the art that every chromatography procedure is strongly dependent on the nature of the chromatography material. For example, fractionation of the negatively charged nucleic acids cannot be achieved by means of a cation exchanger in the pH range indicated. The type of chromatography material (as defined in claim 16) is therefore in this case an essential feature of the method claimed and has to be integrated into the claim.

4.2 It is not clear what is meant by the expression "optionally" in claim 1 (in the case of what circumstances?).